

# UPDATE TO

## Comments on Species Sensitivity Differences

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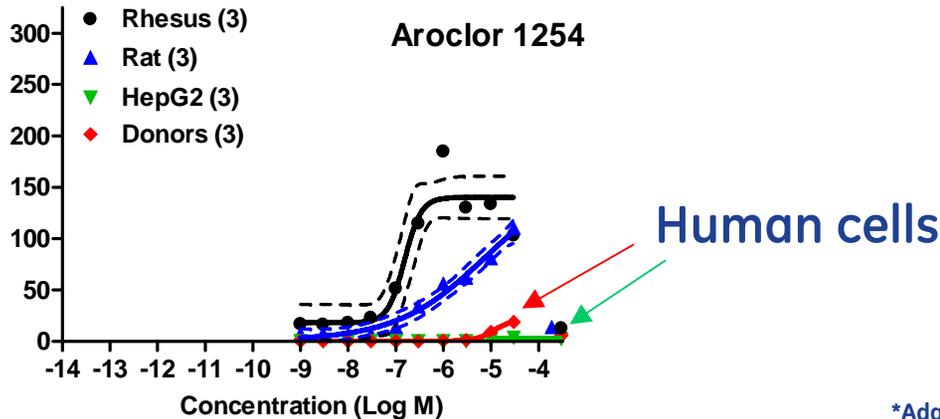
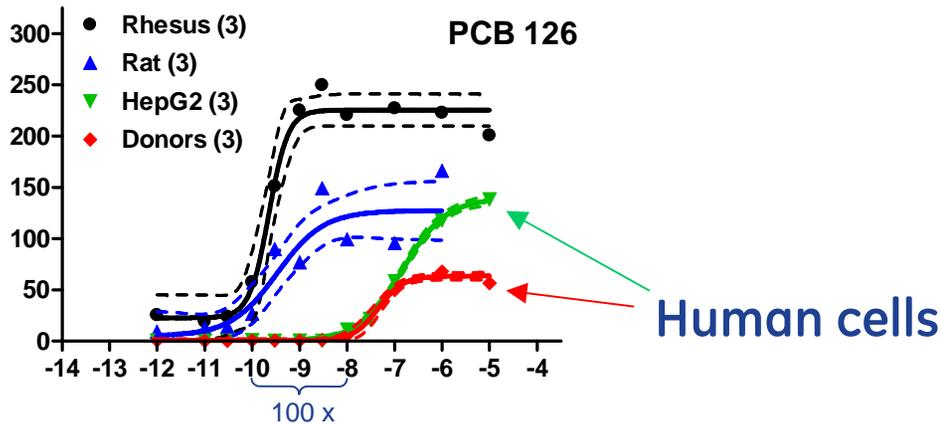
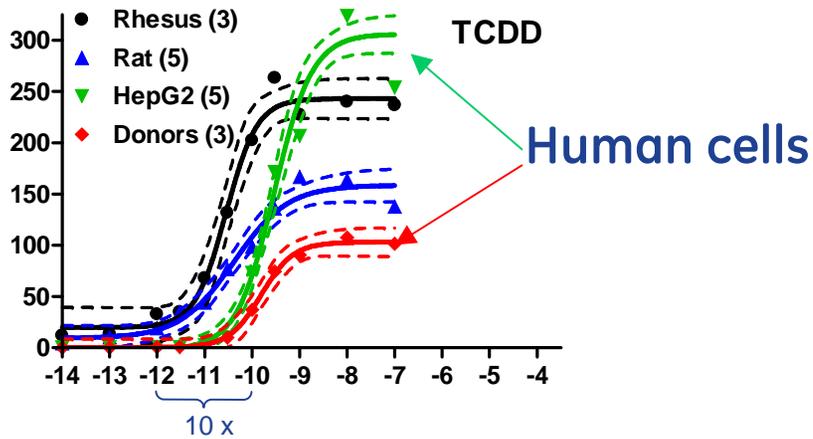
# Application of inconsistently derived risk values

- The Draft Reanalysis uses human data to derive new RfD and CSFs for TCDD only.
- To apply these values to real world mixtures of DLCs, EPA proposes to apply the current WHO TEFs which are derived from rodent studies.
- But, NAS 2006 recommends 'adjusting for species sensitivity differences' if evidence available.
- Some human *in vitro* derived factors are available, e.g., PCB 126 (0.1 in rodents and rodent cells) is 0.002 in human cells. This is a growing and robust data set.

# Hepatocytes

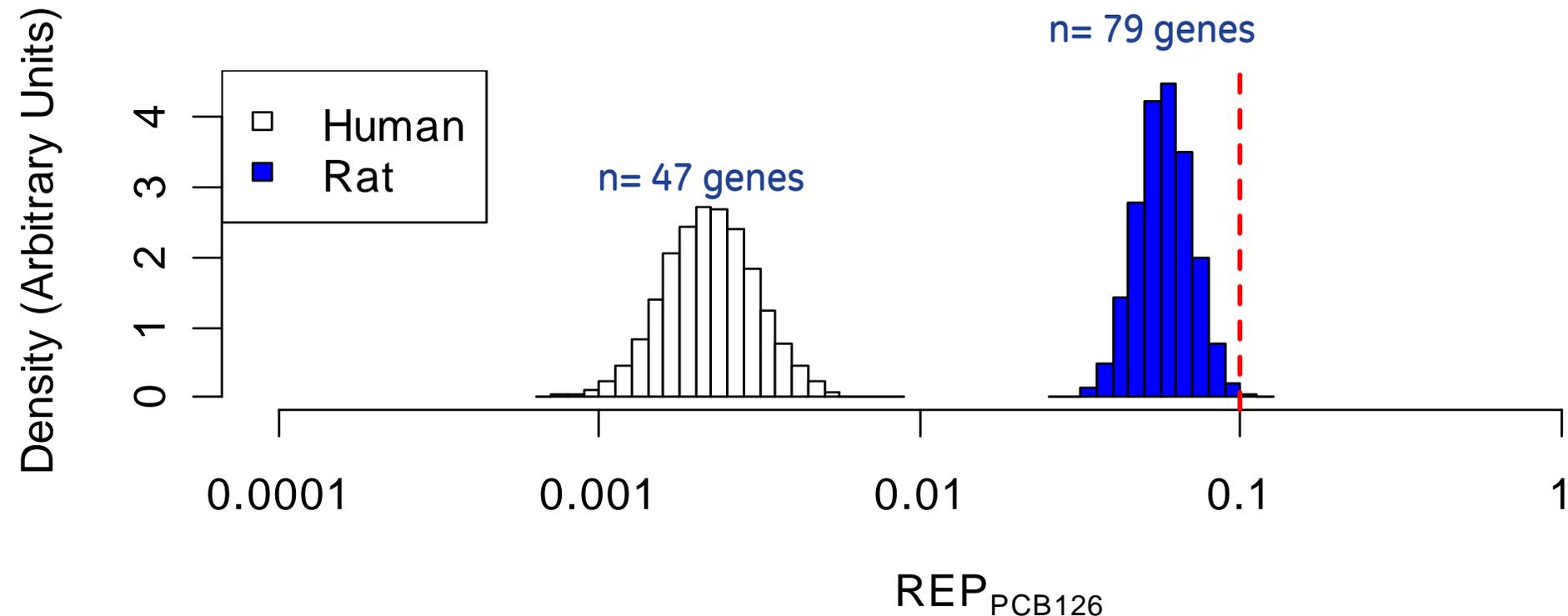
Human cells are ~10x less sensitive to TCDD than rhesus and rat cells to but they are also 100x less sensitive to PCB 126 and Aroclor 1254

Response



# Human insensitivity to PCB126 is true for most responding genes

Toxicogenomic REP modeling



Monte Carlo analysis of distribution around geomean  $REP_{PCB126}$

# Keratinocytes

Show same species sensitivity differences

REP based on EC50s is

0.0027

not 0.1

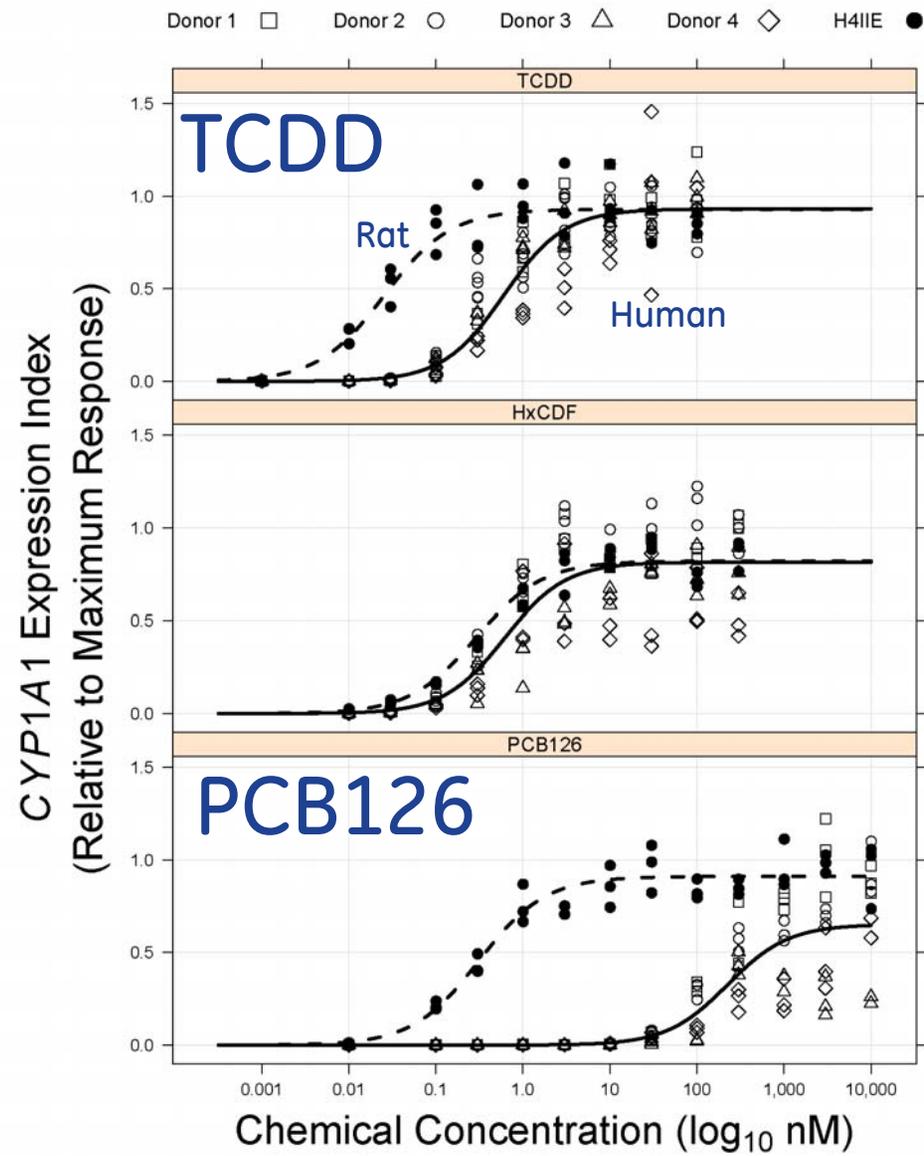


Figure 3

<sup>1</sup>Sutter et al. Tox. Sci. in press, 2010

# Keratinocytes

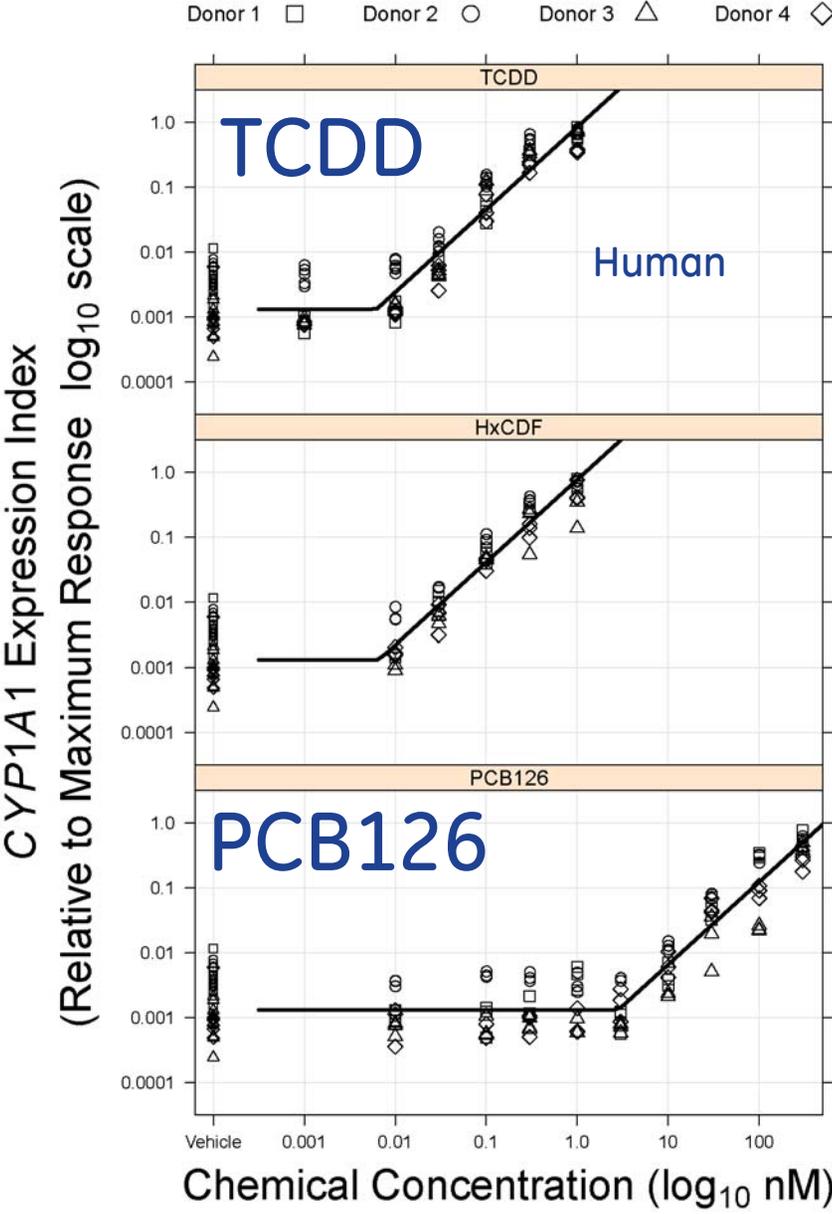


Figure 4

REP based on threshold dose is  
0.0022  
not 0.1

<sup>1</sup>Sutter et al. Tox. Sci. in press, 2010

# Why continue to use rodent-derived TEFs when human-derived REPS are available?

	<u>TEF</u>	<u>REP</u>
WHO TEF (Rodent based )	0.1	
<u>Human</u> Liver		0.002
Keratinocytes <sup>1</sup>		
EC50		0.0027
Threshold		0.0022
Lymphocytes <sup>2</sup>		0.003

<sup>1</sup>Sutter *et al.* Tox. Sci. in press, 2010

<sup>2</sup>van Duursen, *et al.*, Organo Halogens, 2010

# Summary

- Many human genes are far less sensitive than rat genes to these chemicals.
- Chemical potencies of DLCs vary across species.
- Human variability is likely less than inter-species variability.
- Humans genes clearly respond with nonlinear threshold-dependent dose-response curves.
- Animals are not accurately predicting human responsiveness.

Thank you